Please add new claim 41 as follows:

A2

41. The combinatorial library according to claim 1, wherein the combinatorial library is present in an aqueous solution or suspension.

REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants note that non-elected claims 11-40 have been cancelled without prejudice, whereas presently withdrawn claims 8-9 remain pending in this case. Applicants submit that claims 8-9 should be examined together with claims 1-7 and 10, and new claim 41, because the elected species is patentable for the reasons discussed below.

Attached hereto is an Appendix showing the changes made to claims 1-3 and 5-7. The rejection of claims 1-7 and 10 under 35 U.S.C. § 112 (first paragraph) for lack of adequate written description is respectfully traversed.

A first basis of rejection relates to claim 6 and the relationship between the non-biopolymer ligand and the DNA intercalator or major or minor groove binder. By way of the above amendments, claim 1 clarifies that the recognition element is a component of the non-biopolymer ligand. As amended claim 6 presently recites that A^1 is "a non-biopolymer ligand comprising a recognition element selected from the group consisting of a DNA intercalator, a major or minor groove DNA binder, hydroxy groups, pyrrolid-2-yl groups, N-alkylpyrrolid-2-yl groups, alkoxy groups, tetrahydrofuran-2-yl groups, pyrid-2-yl groups, and substituted or unsubstituted phenyl groups." Written descriptive support for this amendment is provided on page 8, line 11 to page 10, line 5.

A second basis of rejection relates to use of the terms "complexing agent" and "non-biopolymer ligand" as well as the relationship between the non-biopolymer ligand and the recognition element.

As to use of the term "complexing agent", claim 1 (and claims dependent thereon) presently recite "metal atom or metal ion" rather than "complexing agent." Applicants submit that adequate written descriptive support is present for the term "metal atom or metal ion" at page 5, line 28 to page 6, line 9 of the present application.

As for the term "non-biopolymer ligand", applicants submit that adequate written descriptive support for this term is present at page 6, line 10 to page 11, line 18 of the present application. Claim 1 presently recites that the "non-biopolymer ligand" includes (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a target molecule. Written descriptive support for these specific limitations is provided at page 6, lines 20-22, and page 8, lines 11-14, respectively. In view of the above amendments, applicants submit that adequate written descriptive support is provided for the non-biopolymer ligands recited in the combinatorial library as presently claimed.

A third basis of rejection relates to the relationship between the "complexing agent" and the "non-biopolymer ligand." As noted above, claim 1 presently recites "metal atom or metal ion" rather than "complexing agent" and specifies that the non-biopolymer ligand comprises "at least one functional group capable of bonding to the metal atom or metal ion." In addition to these limitations, claim 1 further recites that "each of the at least two non-biopolymer ligands is reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond." That the various complexes of the presently claimed combinatorial library are formed by a labile coordinate bond is demonstrated on page 5, lines 21-25; page 17, lines 19-30; and Example 3, which illustrates formation of a combinatorial library of the present invention using a metal ion that forms a coordinate bond. Applicant submit that these limitations overcome the basis for the rejections.

The PTO has taken the position that, because ligand receptor binding is unpredictable, the present application fails to provide the requisite descriptive support for the presently claimed invention. Applicants disagree.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1 "Written Description" Requirement, 64 Fed. Reg. 71427, 71436 (1999). Satisfactory disclosure of a representative

number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Id.

The whole point of the present invention is to provide a combinatorial library that can be readily screened to identify non-biopolymer ligands which bind a target molecule. Inherently, many complexes of the combinatorial library of present invention will not bind the target molecule or will only do so with low affinity; but, as evidenced by the examples provided in the present application, some of the complexes will bind the target molecule with higher affinity. These complexes can then be identified. The exact structure of any particular non-biopolymer ligand is not critical to the presently claimed invention. As claim 1 presently recites, reversible formation of the complex involves the relationship between the metal atom or metal ion and the non-biopolymer ligand. This relationship has been clarified by the above amendments and written descriptive support is provided for each of these amendments.

Moreover, by way of example, the present application identifies 21 sub-genera of non-biopolymer ligands disclosed on pages 6-7. These sub-genera provide numerous individual species which may vary according to the particular functional groups, recognition elements, and (optionally) connectors present in a given non-biopolymer ligand. By virtue of having described a significant number of sub-genera of non-biopolymer ligands, each of which comprises at least one functional group and a recognition element as presently claimed, the present application provides sufficient written descriptive support of the non-biopolymer ligands contained within the combinatorial library of the present invention.

Thus, the combinatorial library itself is adequately described in the present application and one of skill in the art would readily appreciate that applicants were in possession of the presently claimed combinatorial library.

The rejection of claims 1-7 and 10 under 35 U.S.C. §112 (first paragraph) for lack of enablement is respectfully traversed.

The PTO has asserted on pages 6-7 of the outstanding office action a first basis of rejection: that the structure of the non-biopolymer ligands and the complexes which contain them, are essential to enable the claimed invention. Applicants disagree that a specific structure is necessary for the presently claimed invention.

As claim 1 presently recites, complex formation involves the relationship between the metal atom or metal ion and the non-biopolymer ligand, specifically formation of

a labile coordinate bond between the metal atom or metal ion and the functional group of at least two non-biopolymer ligands. The present application identifies a number of different functional groups which can be present on the non-biopolymer ligands, including hydroxyl groups, nitrogen containing groups, and carboxyl groups (page 6, lines 22-25). Once the metal atom or metal ion and the non-biopolymer ligand are introduced together (e.g., in solution or suspension), the complexes self-assemble. Alternatively, individual complexes can be pre-assembled and then introduced together, where they disassemble and self-assemble to form the same or different complexes. Such disassembly and self-assembly is evident from the discussion appearing on page 18, lines 10-22 and page 19, line 10 to page 20, line 22. Thus, one of skill in the art would appreciate that introduction of at least two non-biopolymer ligands (each including at least one functional group) to a metal atom or metal ion, under appropriate conditions (such as those described at page 19, lines 27-31), will yield a combinatorial library of the presently claimed invention.

By virtue of the disassembly and self-assembly of the complexes in the presently claimed combinatorial library, the library itself is capable of undergoing dynamic equilibrium. That is to say, prior to introducing a target molecule into the solution or suspension comprising the combinatorial library of the present invention, an equilibrium will exist among possible complex species in the combinatorial library. By adding a target molecule, an additional equilibrium ensues. This equilibrium involves the binding of complexes to target molecules, with varying degrees of affinity. Since some complexes bind the target molecule with higher affinity than others, those complexes would be depleted from the pool of equilibrating complexes. By simple mass-balance rules, the equilibrium of the complexes would then have to shift in favor of the complexes that bind to the target molecule, effectively using the thermodynamics of ligand-receptor binding to direct the self-assembly of complexes having the highest affinity for the target molecule.

Thus, claim 1 recites all of the requirements of the non-biopolymer ligand which render it capable of forming a labile coordinate bond with the metal atom or metal ion. Applicants submit that neither claim 1 nor claims dependent thereon lack essential subject matter.

The PTO asserts on page 7-8 of the outstanding office action that the pending claims are not enabled, because the various terms recited in the pending claims are purely functional.

As noted above, the pending claims have been amended to replace the term "complexing agent" with "metal atom or metal ion". Therefore, this basis of rejection is overcome.

Also as noted above, the pending claims have been amended to recite structural limitations of the at least two non-biopolymer ligands. Specifically, such ligands include (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a target molecule. The functional group is further defined by the type of bond it forms with the metal atom or metal ion, specifically "a labile coordinate bond". Applicants submit that these structural characteristics are readily ascertained by one of skill in the art. For example, whether a functional group is capable of forming a labile coordinate bond with a metal atom or metal ion can readily be determined by one of skill in the art by reference to standard tables, e.g., Stability Constants of Metal-ion Complexes, Pergamon Press, New York (1979). Many recognition elements are known in the art and, as noted above, are disclosed in the present application.

Contrary to the PTO assertion, applicants submit that the exact structure of any particular non-biopolymer ligand is not critical to the presently claimed invention. This is due to the very nature of the presently claimed combinatorial library. When in the presence of a target molecule, the self-assembly and disassembly of complexes is skewed in favor of the complexes which bind the target molecule with higher affinity (than others in the library). These complexes which bind the target molecule with higher affinity will predominate within the pool of bound target molecules and, thus, can be identified. Hence, the combinatorial library need not include a plurality of complexes each of which binds to a target molecule. Moreover, the ultimate chemical structure can vary widely within the combinatorial library, so long as the recited elements are present on the non-biopolymer ligand–a functional element that allows complex formation with the metal atom or metal ion and a recognition element that allows for binding to a target molecule. Moreover, the above-identified amendments which clarify the nature of the relationship between the metal atom or metal ion and the non-biopolymer ligand make clear the type of combinatorial library being formed.

The structural requirements of the non-biopolymer ligand as presently claimed are illustrated on page 6, line 19 to page 11, line 2. Applicants submit that one of skill in the art can assemble non-biopolymer ligands of the type recited in the presently claimed

invention using commercially available components, known chemical synthesis reactions, or both. Once the non-biopolymer ligands have been prepared they can be introduced to a suitable metal atom or metal ion (disclosed on page 5, line 30 to page 6, line 6), thereby allowing for self-assembly and disassembly of the complexes to occur. Thus, one of skill in the art need only select a metal ion or metal atom and at least two non-biopolymer ligands, and then combine them, to form the combinatorial library as presently claimed.

In view of all of the above, the rejection of claims 1-7 and 10 for lack of enablement should be withdrawn.

The rejection of claims 1-7 and 10 under 35 U.S.C. §112 (second paragraph) for indefiniteness is respectfully traversed in view of the above amendments.

With respect to the term "non-biopolymer ligand", applicants note that this term is defined — for purposes of the present application — on page 6, lines 10-13, which recites "non-biopolymer ligand is meant to include any ligand [which is capable of reversibly binding to the complexing agent, a metal atom or metal ion as claimed,] provided that the ligand is not a DNA molecule, RNA molecule, or polypeptide."

The rejection of claims 1-7 and 10 under 35 U.S.C. §112 (second paragraph) as being incomplete is respectfully traversed in view of the above amendments. As presently claimed, the combinatorial library is formed of complexes that contain a metal atom or metal ion and at least two non-biopolymer ligands. Formation of complexes occurs via formation of a labile coordinate bond between the metal atom or metal ion and at least one functional group of the at least two non-biopolymer ligands. This is clear from the present claims. Therefore, the rejection of claims 1-7 and 10 as being incomplete should be withdrawn.

The rejection of claims 1-7 and 10 under 35 U.S.C. §102(a) as being anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over Klekota et al., "Generation of Novel, DNA-Binding Compounds By Selection and Amplification from Self-Assembled Combinatorial Libraries," Tetrahedron Letters, 38(50):8639-8642 (1997) ("Klekota"), is respectfully traversed.

Klekota is not available as prior art under 35 U.S.C. § 102(a). Pursuant to the accompanying Declaration of Benjamin Miller and Bryan Klekota under 37 CFR § 132 ("Miller and Klekota Decl."), Klekota does not evidence knowledge or use of the present invention by others in this country. Specifically, the presently claimed invention was conceived solely by applicants and experiments were conducted by them or under their

direction (Miller and Klekota Decl., ¶ 3). Under the direction of the applicants, co-author Mark Hammond synthesized some of the initial compounds which applicants used in preparing combinatorial libraries of the presently claimed invention (Miller and Klekota Decl., ¶ 4). Mr. Hammond did not provide any contribution to the conception of the invention as presently claimed (Id.). Thus, Klekota is not available as prior art under 35 U.S.C. § 102(a). Therefore, the rejection of claims 1-7 and 10 is improper and should be withdrawn.

The rejection of claims 1-6 and 10 under 35 U.S.C. § 102(e) as being anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,958,702 to Benner ("Benner") is respectfully traversed.

Benner discloses a combinatorial library which contains two component (Ax and yB), each including a functional group allowing the components to react directly together when presented with a ligand (see column 5, lines 26-61). Example 5 of Benner teaches the preparation of a combinatorial library using a combinatorial library of 1,2 diols in solution with beta lactamase and sodium borate ($NaBO_3$) to yield orthoborate esters and borate esterified with a single diol.

In contrast to Benner, claim 1 presently recites a combinatorial library which includes "a plurality of at least six different complexes, each formed of at least one metal atom or metal ion and at least two non-biopolymer ligands" where each of the non-biopolymer ligands includes "at least one functional group capable of bonding to the metal atom or metal ion" and "a recognition element capable of binding a target molecule." Each of the non-biopolymer ligands "is reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond."

In sharp contrast to the broad disclosure of Benner, the presently claimed combinatorial library requires at least three distinct components: a metal atom or metal ion and two or more non-biopolymer ligands. Benner discloses the use of two functionalized reactants which co-react directly with one another to form various members of a combinatorial library. In Example 5, however, Benner does disclose introduction of a borate ion into a solution which includes a beta lactamase and 1,2 diols, where the 1,2 diols react with the borate ion to form a combinatorial library of borate esters or orthoborate esters. However, this aspect of Benner does not involve a metal atom or metal ion and the combinatorial library does not form a labile coordinate bond with a metal atom or metal ion.

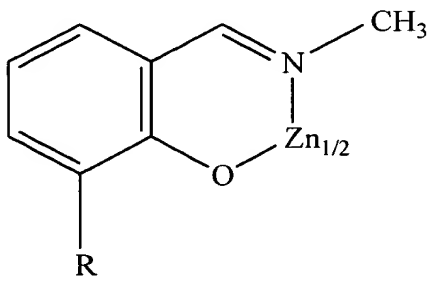
Thus, Benner fails to teach or suggest the preparation of a combinatorial library using a metal atom or metal ion and at least two non-biopolymer ligands each including at least one functional group, where the non-biopolymer ligands are reversibly bonded through the at least one functional group thereof to the metal atom or metal ion by a labile coordinate bond. Because Benner fails to teach each and every element of the presently claimed invention, Benner cannot anticipate claim 1 or claims 2-7 and 10 dependent thereon.

Nowhere does Benner provide any suggestion or other motivation for replacing the borate with a metal atom or metal ion, and the PTO has failed to provide any other motivation in the prior art which would have suggested to one of ordinary skill in the art that it was desirable to do so. Moreover, there is no indication in Benner that the disclosed reaction would be possible were one of ordinary skill in the art to attempt substituting the borate ion with a metal atom or metal ion. This is particularly true, because Benner requires enzymatic (e.g., beta lactamase) activity in order to form the combinatorial library. In view of these deficiencies and the lack of any motivation to modify Benner to arrive at the presently claimed invention, let alone the absence of any expectation of success, claim 1 and claims 2-7 and 10 would not have been obvious over Benner.

In view of all of the above, the rejection of claims 1-7 and 10 over Benner is improper and should be withdrawn.

The rejection of claims 1-7 under 35 U.S.C. § 102(b) as anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over Blackborow et al., "Redistribution Reactions of Some Transition-metal Chelate Complexes. Part III. Exchange in the Zinc Salicylaldimine Series," J. Chem. Res. (S) 119 (1978) ("Blackborow"), is respectfully traversed.

Blackborow generally discloses the ability of salicylaldimines to form monomeric and polymeric complexes with zinc ions (i.e., "salicylaldiminatozinc derivatives" as used by Blackborow). The salicylaldiminatozinc derivatives disclosed in Blackborow have the structure below:



where R is H, methyl, or isopropyl. None of the salicylaldimines of Blackborow contain a recognition element capable of binding a target molecule. This is evidenced by the structure above, where the resulting combinatorial library is devoid of functionality for reacting with a target molecule.

For the reasons noted above, Blackborow fails to teach each and every limitation of claim 1 and claims 2-7 dependent thereon. Therefore, Blackborow cannot anticipate the presently claimed invention.

Moreover, Blackborow contains no suggestion or teaching which would have motivated one of ordinary skill in the art to modify the structures of the salicylaldimines such that the resulting salicylaldiminatozinc derivatives could be made useful as a combinatorial library. Thus, Blackborow cannot have rendered the presently claimed invention obvious.

In view of all of the above, the rejection of claims 1-7 over Blackborow is improper and should be withdrawn.

The rejection of claims 1-7 and 10 under 35 U.S.C. § 102(a) as anticipated by or, alternatively, under 35 U.S.C. § 103(a) for obviousness over WO 98/12156 to Jacobsen et al. ("Jacobsen"), is respectfully traversed.

Jacobsen teaches a combinatorial library which includes a turn element and a plurality of metal-binding groups, whereby the resulting complex is capable of binding a metal ion. The turn element is a "compound[] with defined relative and absolute sterochemistry..." (Jacobsen, page 17, lines 11-16).

Thus, Jacobsen clearly fails to teach a combinatorial library where complexes in the library are formed of a metal atom or metal ion joined by a labile coordinate bond to non-biopolymer ligand(s) containing a recognition element capable of binding a target molecule. Since Jacobsen fails to teach each and every aspect of the presently claimed invention, Jacobsen fails to anticipate the presently claimed invention.

Moreover, Jacobsen clearly teaches away from the present invention. Jacobsen is directed to forming a combinatorial library which is directed to binding a target metal. Nowhere does Jacobsen teach or suggest replacing a turn element thereof with a metal atom or metal ion, as presently claimed. In fact, replacement of the turn element (which is a compound with defined relative and absolute sterochemistry) with a metal atom or metal ion, if it were even possible, would preclude the combinatorial library of Jacobsen from binding

metals as intended. Hence, modifying the combinatorial library of Jacobsen would destroy its function. Thus, because Jacobsen teaches away from the presently claimed invention, Jacobsen cannot have rendered the presently claimed invention obvious.

In view of all of the above, the rejection of claims 1-7 and 10 is improper and should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 18, 2000

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Wendy L. Harrold

1. (Amended) A combinatorial library comprising

a plurality of at least six different complexes, each formed of [at least one complexing agent] a metal atom or metal ion and at least two non-biopolymer ligands each comprising (i) at least one functional group capable of bonding to the metal atom or metal ion and (ii) a recognition element capable of binding a target molecule, wherein each of the at least two non-biopolymer ligands is [that are] reversibly bonded through the at least one functional group thereof to the [complexing agent] metal atom or metal ion by a labile coordinate bond and wherein each different complex in said library has different ligands bonded to the [complexing agent] metal atom or metal ion.

2. (Amended) A combinatorial library according to claim 1, wherein each of said plurality of complexes has the formula $Z(A^i)_n$, wherein Z is [a complexing agent] the metal atom or metal ion [capable of reversibly binding to two or more ligands], each A^i is a non-biopolymer ligand [capable of reversibly binding to Z and is] independently selected from a group of non-biopolymer ligands [having] comprising at least three different members, n is the number of [A's] non-biopolymer ligands [that are] reversibly bonded to [Z] the metal atom or metal ion and is an integer equal to two or greater, and i is an index number for each [A] non-biopolymer ligand and is an integer from 1 to n.

3. (Amended) A combinatorial library according to claim 2, wherein each of said plurality of complexes has the formula $Z(A^1)(A^2)(A^i)_{n-2}$, wherein A^1 and A^2 are non-biopolymer ligands capable of reversibly binding to [Z] the metal atom or metal ion and are independently selected from a group of non-biopolymer ligands having at least three different members and i is an index number for each A and is an integer from 3 to n.

5. (Amended) A combinatorial library according to claim 2, wherein each of said plurality of complexes has the formula $Z(A^1)(A^i)_{n-1}$, wherein A^1 is a non-biopolymer ligand capable of reversibly binding to [Z] the metal atom or metal ion and is independently selected from a group of non-biopolymer ligands having at least three different members; i is an index number for each A and is an integer from 3 to n; and Z, A^1, and each A^i are selected so that the reactions $Z(A^i)_{n-1} + A^1 \rightarrow Z(A^1)(A^i)_{n-1}$ and $Z(A^1)(A^i)_{n-1} \rightarrow Z(A^i)_{n-1} + A^1$ each have a rate constant of greater than about 2 per second.

6. (Amended) A combinatorial library according to claim 2, wherein at least one of A^i is a non-biopolymer ligand comprising a recognition element selected from the group consisting of a DNA intercalator[or], a major or minor groove DNA binder, hydroxy groups, pyrrolid-2-yl groups, N-alkylpyrrolid-2-yl groups, alkoxy groups, tetrahydrofuran-2-yl groups, pyrid-2-yl groups, and substituted or unsubstituted phenyl groups.

7. (Amended) A combinatorial library according to claim 2, wherein [Z] the metal atom or metal ion is a transition metal atom or transition metal ion.